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BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Application Number: 09/293,670
Filing Date: April 16, 1999
Appellant(s): FISHER ET AL.

James Keddie
For Appellant

EXAMINER'S ANSWER

This is in response to the appeal brief filed 11/22/11 appealing from the Office action mailed 7/26/11.

(1) Real Party in Interest

The examiner has no comment on the statement, or lack of statement, identifying by name the real party in interest in the brief.

(2) Related Appeals and Interferences

The following are the related appeals, interferences, and judicial proceedings known to the examiner which may be related to, directly affect or be directly affected by or have a bearing on the Board's decision in the pending appeal:

Appeal No. 2009-015210

(3) Status of Claims

The following is a list of claims that are rejected and pending in the application:

Claims 37-44

(4) Status of Amendments After Final

The examiner has no comment on the appellant's statement of the status of amendments after final rejection contained in the brief.

(5) Summary of Claimed Subject Matter

The examiner has no comment on the summary of claimed subject matter contained in the brief.

(6) Grounds of Rejection to be Reviewed on Appeal

The examiner has no comment on the appellant's statement of the grounds of rejection to be reviewed on appeal. Every ground of rejection set forth in the Office action from which the appeal is taken (as modified by any advisory actions) is being maintained by the examiner except for the grounds of rejection (if any) listed under the subheading "WITHDRAWN REJECTIONS." New grounds of rejection (if any) are provided under the subheading "NEW GROUNDS OF REJECTION."

WITHDRAWN REJECTIONS

The following grounds of rejection are not presented for review on appeal because they have been withdrawn by the examiner: 35 USC §112, 2nd paragraph; 35 USC 112, 1st paragraph as given at page 25 of the final Office action and 35 USC §103 rejections over Uhr et al alone; Uhr et al in view of Hide and Uhr et al in view of Conneally.

(7) Claims Appendix

The examiner has no comment on the copy of the appealed claims contained in the Appendix to the appellant's brief.

(8) Evidence Relied Upon

5612185 UHR 03-1997

WO 97/27212 NOLAN 07-1997

Jia-ping, T., "Multi-parameter sorting technique in flow cytometry" Chinese Journal of Physical Medicine", Vol. 17, no.3, (September 1995), pp. 168-171.

Hide, I. "Degranulation of individual Mast Cells in Response to Ca2+ and Guanine Nucleotides: An All-or-None Event", The Journal of Cell Biology, Vol. 123, Number 3, November 1993 585-593.

Nakanishi, M. "Identification of the active region of the DNA synthesis inhibitory gene p21-sdil/ClP1/WAF1", EMBO Journal, vol.14, no.3, 1995, 555-563.

Tournier, S., "Heterologous Expression of the Human Cyclin-dependent Kinase Inhibitor p21Cipl in the Fission Yeast, Schizosaccharomyces pombe Reveals a Role for PCNA in the chkl+ Cell Cycle Checkpoint Pathway et al", Molecular Biology of the Cell, Vol. 7, April 1996, 651-662.

Polyak, K., "Genetic determinants of p53-induced apoptosis and growth arrest", Genes and Development, vol. 10, 1996, 1945-1952.

(9) Grounds of Rejection

The following ground(s) of rejection are applicable to the appealed claims:

Claim Rejections - 35 USC § 112

Claims 37-44 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

New Matter Rejection

Claim 37 is drawn to a method of screening, comprising: introducing a library of at least 10^3 vectors encoding different candidate agents into a population of mammalian cells grown in vitro; subjecting the population of cells to a physiological signal, wherein said physiological signal stimulates a phenotype in said cells in the absence of the candidate bioactive agents; sorting the individual cells in the population on the basis of at least three optical properties by fluorescent activated cell sorting (FACS), identifying a cell having a phenotype that is altered relative to other cells in the population; and sequencing the nucleic acid encoding said candidate agent in said cell that has an altered phenotype, thereby identifying said candidate agent in said cell.

Claim 37 in its entirety is not supported in the as-filed specification.

Appellants point support for claim 37 in general as found in the specification at page 3, line 36 to page 4, line 5 which discloses:

> In accordance with the objects outlined above, the present invention provides methods for screening bioactive agents for the ability to alter or modulate alterations in cellular phenotypes. The methods generally comprise combining at least one candidate bioactive agent and a population of cells, sorting the cells in a FACS machine by separating the cells on the basis of at least three, four or five cellular parameters. The candidate agents can be part of a molecular library comprising fusion nucleic acids encoding the candidate bioactive agents.

The above-cited section does not support claim 37 in its entirety (i.e., as a unit). It is not clear as to appellants' reference to the support for claim 37 **in general**. Cf. with the claims of the parent issued patent US 6,897,031('031 patent) which finds support in its entirety in specification at e.g., col. 2, lines 22-35. Thus, the present claim is also not supported in the parent application now issued '031 patent.

Applicants cite disparate sections of the specification to provide support for the individual method steps or components in claim 37 as general support, for example:

1. **Mammalian cells grown in vitro:**

Applicants rely at page 10, line 20 of the specification for mammalian cells; for 10^3 library at page 10, line 9 and page 10, lines 10-12 for "*in vitro*" mammalian growth.

The specification at page 10, lines 10-12 recites:

> By a "population of cells" or "library of cells" or "plurality of cells" herein is meant at least two cells, with at least about 10^3 being preferred, at least about 10^6 being particularly preferred, and at least about 10^8 to 10^9 being especially preferred. The population or sample can contain a mixture of different cell types from either primary or secondary cultures although samples containing only a single cell type are preferred, for example, the sample can be from a cell line, particularly tumor cell lines (particularly when as outlined below. The cells may be any cell phase, either synchronously or not, including M, G1, S, and G2. In a preferred embodiment, cells that are replicating or proliferating are used; this may allow the use of retroviral vectors for the introduction of candidate bioactive agents. Alternatively, non-replicating cells may be used, and other vectors (such as adenovirus and lentivirus vectors) can be used. In addition, although not required, the cells are compatible with dyes and antibodies.

There is nothing in the above cited section that recites for mammalian cells grown *in vitro*. The at least 10^3 refers to a **library of cells** and not to a library of **10^3 vectors encoding different candidate agents.** Throughout the specification reference for 10^3 is made for cells. Not a single reference is made in the instant or parent application 09/062330 (now USP 6,897,031) that the vectors are 10^3 library and encoding 10^3

different candidate agents. [Please see also Example 2 which recites a single vector encoding a single agent.]

2. **Physiological signal-** page 9, lines 36-37 and page 34, line 5 which states:

> In another example, the measurements of cell cycle regulation are determined wherein the condition or environment of the populations of cells differs from one another. For example, the cells may be evaluated in the presence or absence of physiological signals, for example hormones, antibodies, peptides, antigens, cytokines, growth factors, action potentials, pharmacological agents (i.e. chemotherapeutics, etc.), or other cells (i.e. cell-cell contacts). In another example, the measurements of cell cycle regulation are determined at different stages of the cell cycle process. In yet another example, the measurements of cell cycle regulation are taken wherein the conditions are the same, and the alterations are between one cell or cell population and another cell or cell population.

The section cited above is the full text since the part of text cited by applicants had been taken out of context. Step 2 of the claim recites "**subjecting** the population of cells to a physiological signal that stimulates a phenotype in cells of the same type in the absence of the candidate bioactive agents".

The specification above recites **evaluating** the cells in the presence or absence of physiological signals, e.g., antibodies or other cells and not of the candidate bioactive agents.

Page 34, line 5 below of the specification presents the same concept.

> For example, the **cells may be evaluated in the presence or absence of physiological signals**, such as **exocytic** inducers (i.e., Ca**, ionomycin, etc.), hormones, antibodies, peptides, antigens, cytokines, growth factors, action potentials, or other cells (i.e. cell-cell contacts). In another example, **the measurements of exocytosis** are determined at different stages of the exocytic process. In yet another example, the measurements of exocytosis are taken wherein the conditions are the same, and the alterations are between one cell or cell population and another cell or cell population. (Emphasis added.)

3. At **least three optical properties** - page 4, line 3 of the specification recites:

> The methods generally comprise combining at least one candidate bioactive agent and a population of cells, sorting the cells in a FACS machine by, separating the cells on the basis of at least three, four or five **cellular parameters.** (Emphasis added.)

The reference is made to at least three **cellular parameters** but not to the claimed at least three optical properties as in claim 37.

The specific optical properties are alleged to find support at page 34, lines 30 and 37:

> In a preferred embodiment, changes in light scattering are assayed to determine alterations in exocytosis in a population of cells. When viewed in the FACS, cells have particular characteristics as measured by their forward and

> 90 degree (side) light scatter properties. These scatter properties represent the size, shape and granule content of the cells. Upon activation of the cells with a pro-exocytic stimulus, both the forward and side scatter properties of the cells changes considerably. These properties account for two parameters to be measured as readout for the exocytic event. These properties change in proportion to the extent of exocytosis of the cells and depend on the time course of the exocytic events as well. Alterations in the intensity of light scattering, or the cell-refractive index indicate alterations in exocytosis either in the same cell at different times..

This section provides support for only two optical properties i.e., forward and side and for exocytosis phenotype and not any other cell phenotypes, as in claim 37.

4. **Sequencing to identify - page 28, lines 10-12 recites:**

> In a preferred embodiment, the fusion partner is a rescue sequence. A rescue sequence is a sequence which may be used to purify or isolate either the candidate agent or the nucleic acid encoding it.

This section presents a different concept and relates to a different compound, fusion partner. The claim is to a sequencing steps or procedures by which the presumably isolated and identified agent is sequenced. Because the specification, even the above quoted support, does not disclose a single candidate

agent that has been isolated and identified hence, it is not seen how sequencing can occur.

Accordingly, claim 37 in its entirety or the disparate sections cited by applicants do not lend support for the present [amended] claims. Claims in its entirety should appear in the specification as in the claim. Picking and choosing disparate sections in the specification to support the individual element of the claims leads to a claim that is loosely connected and as the elements themselves do not find support in the as-filed specification. Cf. with the claims of the parent issued patent US 6,897,031(‘031 Patent) which finds support in its entirety in specification at e.g., col. 2, lines 22-35. Thus, the present claim is not also supported in the parent application, now the issued ‘031 Patent.

Written description Rejection

Claims 37-44 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

To satisfy the written description requirement, an applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention.

Applicants are not in possession of the claim method in its entirety as recited in claim 37. The specification at the time of filing does not describe a library of 10^3 vector encoding presumably also 10^3 different kinds of candidate agents. It does not describe whether the library of 10^ vectors are of the same or different type that would encode a 10^3 [any] different kind of candidate agents. Since there is no description of a library of 10^3 vectors hence, there is no description of a candidate agent that has been isolated or identified by the encoded diverse library of 10^3 vectors where the candidate agents alter a phenotypic change to a population of mammalian cells. Throughout the specification description of 10^3 library is to cells but not to library vector that encodes (absent any gene or nucleic acid therein) an enormous numbers (10^3) of different kinds of candidate agents. The working example in the specification describes the effect of a single known candidate agent p21 and its phenotypic effect to a population of 10^3 cells. There is no description of whether the single known p21 has been selected, purified and identified from the 10^3 library

of vectors. Nor is there a description of an isolated and identified candidate agent that alters any or all kind(s) of phenotypes in a population of cell. Since no identification of a candidate peptide agent has been made and the single protein (not peptide) is known hence, it is not readily apparent how sequencing can be done to an already known protein. There are no characterizing features of the genus candidate agent coupled with a functional limitation or core sequences corresponding with the single protein described in the specification to lead a skilled artisan to the general method.

Enablement Rejection

Claims 37-44 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method using a single protein, does not reasonably provide enablement for claim 37 method using a library of 10^3 vectors and the other claim parameters (as given in the new matter rejection above). The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The enabling disclosure provided in the specification is not commensurate in scope with the recited general method. The method employs broadly a huge 10^3 library vectors encoding directly any different candidate agent that affects any phenotype of a cell in a population. The specification provides only broad generalized statements. It would take an undue amount of experimentation to determine the 10^3 library of vectors encoding different candidate agents that alters any type of phenotype in a cell(s) population. This is made more complex since the specification does not provide support for the claim general method. (Please see the new matter rejection above.)

The factors that are to be considered in the determination of undue experimentation are disclosed in In re Wands, (U.S.P.Q. •2d 1400 (CAFC 1988). These include: the quantity of experimentation necessary, the amount of direction or guidance presented, the presence or absence of working examples, the nature of the invention, the state of the art, and the predictability of the art and the breadth of the claims.

1). The specification fails to give adequate direction and guidance in how to make the 10^3 library of vectors encoding any candidate agent(s). The specification describes only a 10^3 library of cell population. Therefore, the specification does not teach how to go about making a vectors of 10^3 library of

different kinds encoding different kinds of candidate agents. The specification does not describe from the 10^3 library the candidate agent that has phenotypically alter a population of cells to enable its isolation, identification and sequencing.

2). Applicants have failed to provide any working examples for a 10^3 library of any kind of vectors, whether the same or of different type encoding an enormous diverse kinds of candidate agents that alter a number of phenotypes of a cell population. The working example provides for a single, known protein p21. It is not apparent from the specification whether this single, known protein is the one obtained from the encoding library of vectors, isolated from the rest of the cells, identified and sequenced.

3). The state of the prior art is such that the consequences of some bioactive agent and cell interaction on some cells have not yet been fully determined or elucidated. See Polyak (Genes and Development) at e.g., page 1945, col. 2.). The art is inherently unpredictable with respect to the numerous types of agents altering even a single phenotype of a single cell let alone a population of cells. Also, the use of a wide variety of libraries with candidate agent presentations can be

displayed in an extraordinarily large number of conformations. See Nakanishi (The EMBO Journal) e.g., at page 556, col. 2, last paragraph and Tournier et al (Molecular Biology of the Cell) e.g., at page 658, col. 2). The breadth of the claims encompasses large possible combinations for the different unnamed or undefined variables of library of vectors, candidate agents, phenotypes and cell population.

6). While the level of skill in the art is high, the molecular biology and gene art is so unpredictable that it would require undue experimentation to make the invention commensurate in scope with that claims in the absence of adequate guidance or direction as set forth above. This is especially true when the present claim described in general terms which are not supported in particular by the specification. The specification provides only definitions of the terms use in the general method. For example, at page 16, line 8 up to-page 30, line 15 the term "candidate bioactive agent" is defined as a diverse molecules, e.g., protein, small organic molecule, carbohydrates (including polysaccharides), polynucleotide, lipids, etc.

Appellants' disclosure would not enable a skilled artisan to carry out the claimed methods without undue experimentation as the claims in general or elements of the claims in particular have not been enabled.

Claim Rejections - 35 USC § 103

Claims 37 and 40-44 are rejected under 35 U.S.C. 103(a) as being obvious over Nolan in view of Jia-ping and Uhr et al.

Nolan et al discloses at e.g., page 31, line 1 up to page 32, line 6; a method comprising introducing a molecular library of randomized candidate nucleic acids into a plurality of cells, a cellular library. Each of the nucleic acids comprises a different, generally randomized, nucleotide sequence. The plurality of cells is then screened for a cell exhibiting an altered phenotype. The altered phenotype is due to the presence of a transdominant bioactive agent. Any phenotypic change may be observed, detected, or measured on the basis of the screening methods. Suitable phenotypic changes include, but are not limited to gross physical changes such as changes in cell morphology, cell growth (cell cycle, as claim), cell viability (apoptosis, as claim), changes in the expression of one or more RNAs, proteins, changes in the localization of one or more RNAs, proteins, changes in the bioactivity or specific activity of one or more RNAs, proteins, changes in the secretion of ions, cytokines, hormones, growth factors, or other molecules and etc. (reads on the claim physiological signal). The altered phenotype is detected in a wide variety of ways and will generally depend

and correspond to the phenotype that is being changed. Generally, the changed phenotype is detected using, for example, Standard cell viability assays, including both increased cell death and increased cell viability, for example, cells that are now resistant to cell death via virus, bacteria, or bacterial or synthetic toxins; standard labeling assays such as fluorometric indicator assays for the presence or level of a particular cell or molecule, including FACS or other dye staining techniques; biochemical detection of the expression of target compounds after killing the cells. Once a cell with an altered phenotype is detected, the cell is isolated from the plurality which does not have altered phenotypes. This may be done in any number of ways, as is known in the art, and will in some instances depend on the assay or screen. Suitable isolation techniques include, but are not limited to, FACS or other cell vitality indicator dyes.

Nolan does not disclose a method in which the cellular phenotype is exocytosis and at least 3 optical parameter cell sorting by FACS (although suggests said FACS analysis). However, Jia-ping discloses a method of sorting cells by multi-parameter sorting technique using flow cytometer including exocytosis. The method provides for an increase of purity of the divided cell

and further information of the different cell subpopulations (page I).

Uhr discloses at e.g., col. 3, line 50 up to col. 4,line 37; a method of identifying a candidate substance, capable of inducing alteration of cellular phenotype comprising contacting the population of cells to be analyzed with a panel of (library of candidate agents) directed against distinct cell surface molecules, under conditions effective to allow antibody binding. The antibodies would be labeled in a manner to allow their subsequent detection, such as by tagging with a fluorescent label. By using fluorochromes that can be excited by 2 different lasers to give off light at 4 different wavelengths (reads on the claim at least 3 optical parameters), it is possible to use 4 distinct antibodies to 4 different surface antigens and, in addition, to use 2 light scattering parameters, direct and orthogonal (reads on claim 40). Thus cells can be separated on the basis of 6 parameters. The population of tumor cells with bound antibodies may then be separated by cell sorting, preferably using **fluorescence-activated flow cytometry**. Uhr discloses that for multiparameter cell sorting, it is contemplated that one would wish to employ a combination of agents that results in independent signals of 4 different

wavelengths. This may be readily achieved by using four distinct monoclonal antibodies. Alternatively, the fourth signal may be supplied by employing a DNA stain which results in color generation, such as Hoechst, and in these circumstances only three monoclonal antibodies may be used in the separation procedure. Uhr further discloses at e.g., cols. 7-14, Table 1 the panel of antibodies. Uhr discloses or suggests at e.g., col. 22, lines 14-20 the preparation of vectors which incorporate nucleic acid sequences capable of encoding the desired genes introduced into the cells to be treated. The replication defective retrovirus (reads on claim 43) may be used, as may other vectors. Fig. 1 discloses that Flow cytometry was performed on a FACS wherein forward light scattering, orthogonal light scattering, FITC and PE signals were determined for 30,000(3 x10^4) cells. FIG. 3 shows cDNA synthesized from a mixture of 10^4 cell-equivalents of total RNA and 10^6 (myc and fos panels) or 10^7 (actin panel).

It would have been obvious to one having ordinary skill in the art at the time the invention was made to determine the changes in the exocytosis phenotype of a cell by at least 3 optical parameters in the method of Nolan in the manner as taught by Jia-ping and Uhr. One having ordinary skill in the art

would have been motivated to sort the alteration in the phenotypic cells by at least 3 parameters based on exocytosis phenotype of the cell for the advantages taught by Jia-ping and Uhr. The alteration in the exocytosis phenotype of the cell provides further information of the different cell subpopulations such that an increased purity of the divided cell is obtained.

Claims 38 and 39 are rejected under 35 U.S.C. 103(a) as being unpatentable over Nolan in view of Jia-ping and Uhr et al as applied to claims 37 and 40-44 above, and further in view of Hide et al.

Nolan is discussed above. Nolan discloses a FACS means of measuring the altered cellular phenotype but not exocytosis induced by Ca++ or ionomycin.

Hide discloses e.g., at page 588, col. 2 that cells contain large numbers of secretory granules which makes them highly refractile as manifested in the light-scattering properties of the cells, particularly at around 90 degrees. When the cells have undergone exocytosis, their refractivity is lost and their ability to scatter light at 90 degree is correspondingly diminished. This attribute has been used to classify populations of cells. Hide further discloses at e.g., page 592 that a

suboptimal concentration of the stimulus ionomycin will distinguish between populations of cells that have differing thresholds to stimulus intracellular Ca++. The strength of the stimulus selects the cells which then proceed to a full degranulation. It would have been obvious to one having ordinary skill in the art at the time the invention was made to measure the cellular phenotype alteration in the method of Nolan by exocytosis using such stimulus as Ca++ or ionomycin as taught by Hide. Hide teaches that exocytosis measurement when stimulated by Ca++ or ionomycin will distinguish between populations of cells that have differing thresholds. The strength of the stimulus would select the cells which then process to full exocytosis. One would have been motivated to use stimulus as Ca++ or ionomycin to differentiate one cell from another by the effect of the stimulus. One would have a reasonable expectation of success since exocytosis phenotype has been used to differentiate cells in a population using FACS.

(10) Response to Argument

35 USC 112, New Matter Rejection

Appellants present the Table at page 7 of the Brief for an element to element support for the pending claims. For example

claim 37, general support for screening method at page 3, line 36 to page 4, line 5.

In reply, page 3, line 36 to page 4, line 5, discloses:

> In accordance with the objects outlined above, the present invention provides methods for screening bioactive agents for the ability to alter or modulate alterations. The methods generally comprise combining at least one candidate bioactive agent and a population of cells, sorting the cells in a FACS machine, separating the cells on the basis of at least three, four or five cellular parameters. The candidate agents can be part of a molecular library comprising fusion nucleic acids encoding the candidate bioactive agents.

Cf. with the generic claim method of claim 37 drawn to a method of screening, comprising: introducing a library of at least 10^3 vectors encoding different candidate agents into a population of mammalian cells grown in vitro; subjecting the population of cells to a physiological signal, wherein said physiological signal stimulates a phenotype in said cells in the absence of the candidate bioactive agents; sorting the individual cells in the population on the basis of at least three optical properties by fluorescent activated cell sorting (FACS), identifying a cell having a phenotype that is altered relative to other cells in the population; and sequencing the nucleic acid encoding said candidate agent in said cell that has an altered phenotype, thereby identifying said candidate agent in said cell.

Thus, page 3, line 36 to page 4, line 5 do not provide support for the generic claim method, as a whole. This section does not only support claim 37 as a whole, but also does not support the claim elements e.g., at least 10^3 vectors encoding different candidate agents into a

population of mammalian cells grown in vitro, as argued by appellants.

Appellants argued that the different elements of the method are supported in the specification as follows:

Mammalian cells grown in vitro

Appellants argue that the method can be done using mammalian cells is explicitly described on page 10, line 20, of the instant application:

> Preferred cell types for use in the invention will vary with the cellular phenotype to be modulated. Suitable cells include, but are not limited to, **mammalian cells**, including animals {rodents, including mice, rats, hamsters and gerbils), primates, and human cells, particularly including tumor cells of all.

Appellants further argue that the method can be done using cells grown in vitro is explicitly described at page 10, lines 10-14 of the instant specification:

> 10^8 to 10^9 being especially preferred. The population or sample can contain a mixture of different cell types from either primary or secondary cultures although samples containing only a single cell type are preferred, for example, the sample can be from a cell line, particularly tumor cell lines (particularly when, as outlined below). The cells may be in any cell phase, either synchronously or not, including M

In reply, the above sections taken out of context from the full text, (see the text of page 10, lines 8-10) relates to a population of cell types from either a primary or secondary cultures, and not to a library of 10^3 vectors transfected into the cells grown in vitro.

Appellants argue that the method can be done using a library of at least 10^3 vectors is implicitly supported in the priority application at page 10, lines 8-10 (which states that the candidate agent may be contacted with at least 10^3 cells) in combination with page 21, lines 1-2 (which states that the cells may contain a single vector).

Page 10, lines 8-10 of the instant application, which states that the candidate agent may be contacted with at least 10^3 cells, is set forth below:

> By a "population of cells" or "library of cells" or "plurality of cells" herein is meant at least two cells, with at least about 10^3 being preferred, at least about 10^6 being particularly preferred, and at least about 10^8 to 10^9 being especially preferred. The population or sample can contain a mixture of different cell

and page 10, lines 8-10(sic, page 21, lines 1-2) which states that the target cells may contain a single vector, is set forth below

> In addition, it is possible to configure a retroviral vector to allow inducible expression of retroviral inserts after integration of a single vector in target cells: importantly, the entire system is contained within the single retrovirus. Tet-inducble retrovirus have been designed incorporating the self-

Appellants argue that if there are at least 10^3 cells each containing a single vector, then there is implicit support for 10^3 vectors. Appellants further note that the introduction of libraries of agents of various complexities into a population of cells is discussed on page 19 of the specification.

In reply, the above section states integration of a single vector in target cells. This is contrary to Appellants' equation or assumption that if there are at least 10^3 cells each containing a single vector, then there is implicit support for 10^3 vectors. Claim 37 recites "introducing a library of at least 10^3 vectors encoding different candidate agents into a population of mammalian cells". The claims do not recite a single cell with a single vector member of a library and the claims do not recite a target cell. Please note Example 2 which teaches a single vector encoding a single agent(not 10^3 population of agents) into a population of cells which also contradicts appellants' above conclusion.

Appellants further note that the introduction of libraries of agents of various complexities into a population of cells is discussed on page 19 of the specification. Based on the above, the phrase "at least 10^3 vectors encoding different candidate agents into a population of mammalian cells grown in vitro" is fully supported in the instant application.

In reply, page 19 of the specification recites in part:

> In a preferred embodiment, a library of different candidate bioactive agents is used. Preferably, the library should provide a sufficiently structurally diverse population of randomized agents to effect a **probabilistically** sufficient range of diversity to allow binding to a particular target. Accordingly, an interaction library should be large enough so that at least one of its members will have a structure that gives it affinity for the target. Although it is difficult to gauge the required absolute size of an interaction library...(Emphasis added.)

Thus, these general statements of "libraries of agents of various complexities" do not lend support for the library of 10^3 vectors encoding different bioactive agents.

Specific argument directed to claim 41

Appellants argue that to the extent that the argument set forth immediately above is not persuasive and this rejection is to be maintained because there is no explicit support for "10^3 vectors", the Appellants submit that explicit support for claim

41, which requires a library "of at least 10^6 vectors" is found on line 20 of page 19. This section states that, in the context of a library, "at least 10^6… different sequences are simultaneously analyzed in the subject methods".

In reply, the new matter issue is not only in reference to the single element contain in the method of claim 37. Rather, claim 37 as a whole, which appellants provide support by carving out the terms(elements) from the disparate sections of the specification. "At least 10^6 vectors" as the specification teaches at page 19, line 20 states is only **probabilistically and the absolute size is difficult to gauge.**

Physiological signals

The Appellants submit that evaluating cells in the presence or absence of a physiological signal implicitly requires that the cells are subjected to a physiological signal. As such, "subjecting" a population of cells to a physiological signal is implicitly supported in the specification.

In reply, "evaluating" is not an implicit teaching of "subjecting", as argued. The claims present a different concept from that taught in the specification as stated above under the grounds of rejection. The claims recite "subjecting the cells to a physiological signal stimulates a phenotype in said cells in

the absence of the candidate agents". While the specification teaches that the cells are evaluated in the presence or absence of a stimulus as exocyotosis. Because each of the elements are obtained from different sections of the specification hence, claim 37 as a whole does not have logical sense.

At least three optical properties

Appellants argue that the cellular parameters by which a cell is sorted are in fact optical properties. See, e.g. the entire application particularly the context given on page 34, lines 30-37, which states that parameters that are characteristic of a cell are measured by light scatter properties. Moreover, in the flow cytometer arts (and consistent with how the term is used in the instant application) a "parameter" corresponds to an optical property (e.g., fluorescence, side scattering, etc.). In view of the above, the Appellants submit that the cited support (which recites "at least three, four or five cellular parameters") provides more than adequate support for the phrase "at least three optical properties" as claimed.

In reply, as correctly stated by applicants, page 34, and lines 30-37 recite only light scatter properties, not the claim "optical". The claims recite that the optical properties are

sorted by FACS and not that the FACS parameters are applied to sort the claim three optical properties.

The argued various parameters are not commensurate in scope with the claim 3 optical properties.

The test whether or not the amendment constitutes new matter is whether or not the claim limitations would indicate to one skilled in the art that the inserted step(s) formed part of applicants' original disclosure (invention), not that it is known in the art.

Sequencing to identify

Appellants argue that in the section bridging pages 7 and 8, the Examiner states that the cited passage on page 28, lines 10-12 does not provide support for the last element of the claims, i.e., sequencing the nucleic acid. Supplemental support for this element is found on page 32, lines 34-36, as shown below:

> In a preferred embodiment, the bioactive agent is characterized. This will proceed as will be appreciated by those in the art, and generally includes an analysis of the structure, identity, binding affinity and function of the agent. Generally, once identified, the bioactive agent is resynthesized.

Appellants submit that because the structure of a nucleic acid is defined by its nucleotide sequence, the "analysis of the structure" of a nucleic acid provides implicit support for sequencing the nucleic acid.

In reply, the above section does not recite the claim sequencing step. Because there is no structure hence, no sequencing has occurred. Analysis of the structure is not necessarily sequencing of the structure. The structure can be analyzed in terms of the atoms present or arrange in the molecule as its tertiary structure. The specification does not describe a single compound from the 10^3 library that has been sequenced since no structure of any nucleic acid has been identified.

35 USC 112, Written Description Rejection

Response to Arguments

Appellants traverse to the extent that this rejection is not already addressed in the Appellants' traversal of the new matter rejection above. The Appellants submit that the instant specification is replete with description about how the claimed method may be performed. See, e.g., pages 8-41. With specific reference to the libraries of vectors (which appears to be a focal point for the Examiner), the Appellants submit that such

libraries are generically described in the instant specification at, e.g., page 19, line 31 to page 21, line 11. Moreover, libraries of vectors are conventional in the art (see, e.g., WO97/27212), which is cited by the Examiner in an obviousness rejection that is discussed below. Thousands of other publications describe the production and use of libraries of vectors. Since the guidelines clearly state that "the description need only describe in detail that which is new or not conventional" and "What is conventional or well known to one of ordinary skill in the art need not be disclosed in detail", there is no need for the Appellants to provide a detailed description of libraries of vectors that can be used in the rejected claims. Moreover, the candidate agents recited in the claims are not required to perform any specific function or to have any particular structure. There is no need to describe the specific function or particular structure of something that does not need a specific function or particular structure to work. Finally, to the extent that this rejection is based on the lack of a reduction to practice (see further comments on page 16 of the Office Action, e.g., "no identification of a candidate peptide agent has been made"), the Appellants submit that even in the biotechnology arts a reduction to practice is not required for written description. See MPEP § 2163: "(1) examples

are not necessary to support the adequacy of a written description; (2) the written description standard may be met even where actual reduction to practice of an invention is absent; and (3) there is no per se rule that an adequate written description of an invention that involves a biological macromolecule must contain a recitation of known structure." Citing Falkner v. Inglis, 448 F.3d 1357, 1366, 79 USPQ2d 1001, 1007 (Fed. Cir. 2006). See also Capon v. Eshhar, 418 F.3d at 1358, 76 USPQ2d at 1084.

In reply, the general term “library of vectors” is nothing more than a general term as known in the art. Appellants have not proffered a single prior art that teaches a library of 10^3 vectors that encode 10^3 candidate agents especially as applied in the context of the claim method (which appellants alleged is novel). Since the library of vectors of 10^3, encoding 10^3 different candidate agents are not supported by the as-filed disclosure, hence the written description requirement is not met. See, e.g., In re Lukach, 442 F.2d 967, 169 USPQ 795 (CCPA 1971). MPEP 2163.

As addressed above under the new matter rejection, library of 10^3 candidate agents is not the focal point of the rejection rather the claim in its entirety. But since appellants have

relied on different, loosely connected elements as support of claim 37, the library of 10^3 vectors is but one of these elements. Since there is no support in the specification, clearly there cannot be a written description.

The Federal Circuit has cautioned against over reliance on the assertion that everything needed to practice the full scope of the claims was "known in the art" and that a patent need not teach, and preferably omits, what is well known in the art. See Genentech Inc. v. NovoNordiskA/S, 108 F.3d 1361, 1366, 42 USPQ2d 1001, 1005 (Fed. Cir. 1997): "[T]hat general, oft-repeated statement is merely a rule of supplementation, not a substitute for a basic enabling disclosure. It means that the omission of minor details does not cause a specification to fail to meet the enablement requirement (written description).... It is the specification, not the knowledge of one skilled in the art that must supply the novel aspects of an invention in order to constitute adequate enablement."

Here, the specification does not teach the method steps (alleged to be novel) and the elements/components use in the method such as the broad 10^3 vectors encoding candidates agents transfected into any mammalian cells in vitro to identify and sequence the candidate agent. Appellants point to nothing in the specification that would indicate to the contrary.

The single working example negates the claim method since the single element 10^3 libraries (collection) of different candidate agents of the method are based only on the description of the single known p21 protein.

Specific argument directed to claim 41

Appellants argue that if the above is not persuasive and this rejection is to be maintained because there is inadequate written description for "103 vectors", the Appellants submit that explicit support for claim 41, which requires a library "of at least 10^6 vectors" is found on line 20 of page 19. This section states that, in the context of a library, "at least 10^6 different sequences are simultaneously analyzed in the subject methods". Thus, if the Board believes that the rejection of claim 37 should be maintained because the specification does not describe 103 vectors, the Board is requested to withdraw the rejection of claim 41.

In reply, the same reasons above are incorporated herein, in its entirety, since appellants merely present the same arguments as above.

35 USC 112 Enablement Rejection

Response to Arguments

Appellants request the Board to apply the arguments in the prior section of this response to this rejection. Specifically, the Appellants submit that libraries of vectors are conventional in the art and, as such, their making and use does not require undue experimentation. Moreover, the candidate agents recited in the claims are not required to perform any specific function or to have any particular structure. There is no need to describe the specific function or particular structure of something that does not need a specific function or particular structure to work. Furthermore, pre-knowledge of the structure and function of the candidate agents would undermine the purpose of the invention. Moreover, to the extent that this rejection is based on the lack of a reduction to practice (see further comments on page 23 and 24 of the Office Action, e.g., "The single working example teaches ...."and "There is not a single working example", the Appellants submit that even in the biotechnology arts a working example is not required for enablement. See MPEP § 2164.02: "Compliance with the enablement requirement of 35 U.S.C. 1127 first paragraph does not turn on whether an example is disclosed." The vast amount of guidance in the instant

application, combined with what is already routine in the art, should enable the appealed claims.

In reply, the same reasons above are incorporated herein in its entirety, since appellants present the same arguments as above.

Because there is no support for claim 37 method, e.g., the library of 10^3 vectors from which a candidate agent is to be identified, sequenced and determined for its phenotypic effect on the cells, how the library is made is therefore clearly lacking.

The claims recite for identifying a candidate agent from the 10^3 vectors, but not a single 10^3 vectors of candidate agents have been made. Claims are not read in vacuum but in light of the specification. The specification teaches throughout that the candidate agent is a single agent. If the specification does not provide enabling disclosure for the claim candidate agents, its identification and structure as claimed, then it not clear as to the argued "vast amount of guidance in the instant application, combined with what is already routine in the art". Appellants have not proffered a single reference that a 10^3 vectors with 10^3 candidate agents are known in the art and as specifically applied to the alleged novel method. Attention is drawn to Nakanishi et l (EMBO Journal) e.g., at page 556, col.

2, last paragraph and Tournier et al (Molecular Biology of the Cell) e.g., at page 658, col. 2) which all contradict appellants' arguments.

35 USC 103 Rejection

Nolan in view of Jia-Ping and Uhr.

The Appellants submit that Nolan cannot preclude the patentability of the rejected claims for the reasons set forth below (see the arguments under new matter rejection). Appellants state that the instant application's earliest priority date is April 17, 1998, as indicated on the filing receipt and the application data sheet of this application. The relevant section of the filing receipt is reproduced below for the Board's convenience.

Domestic Priority data as claimed by applicant.

> This application is a CIP of 09/157, 748 09/21/1998 PAT 6,461,813 which is a CIP of 09/062,330 04/17/1998 PAT 6,897,031

Thus, the instant application claims priority to an application (09/062,330) that was filed on April 17, 1998. Appellants present the table at pages 23-24 that indicates support for the rejected claims in the instant application, and in the parent application.

Appellants argue that Nolan's publication date (July 31, 1997) predates the earliest priority date of this application

(April 17, 1997) by less than a year. As such, Nolan only qualifies as prior art only under 35 U.S.C. § 102(a)

A Declaration under 35 U.S.C. § 1.131 (the "Fisher Declaration"; submitted herein in the Evidence Appendix of this brief) was submitted with the Appellants' response dated July 24, 2006, in order to obviate a rejection over a similar combination of references (i.e., Nolan in view of Jai-ping or Ryan). The Fisher Declaration establishes invention of the subject matter of the rejected claims prior to the Nolan's publication date and, as such, Nolan cannot preclude the patentability of the instant claims.

Support for each element of the claims in the priority application is provided in the table at pages 23-24. Exemplary support for each of the four elements that the Examiner has an issue with is discussed below:

"A library of at least 10^3 vectors"

That the method can be done using a library of at least 10^3 vectors is implicitly supported in the priority application at page 24, lines 24-27 (which states that the candidate agent may be contacted with at least 10^3 cells) in combination with page 22 lines 17 and 18 (which states that the cells may contain

a single vector). If there are at least 10^3 cells each containing a single vector, then there is implicit support for 10^3 vectors.

Page 24, lines 24-27 of the priority application, which states that the candidate agent may be contacted with at least 10^3 cells, is set forth below:

> The candidate bioactive agents are combined or added to a cell or population of cells. Suitable cell types for different embodiments are outlined above. By "population of cells" herein is meant at least two cells, with at least about 10^3 being preferred, at least about 10^ being particularly preferred, and at least about 10^3 being especially preferred.

and page 22 lines 17 and 18, which states that the target cells may contain a single vector, is set forth below:

> In addition, it is possible to configure a retroviral vector to allow inducible expression of retroviral, inserts after integration of a single vector in target cells; importantly, the entire

Based on the above, the Appellants submit that the phrase "at least 10^3 vectors encoding different candidate agents" is fully supported in the priority application.

In reply, the filing date of the instant application is April 16, 1999 (see Transmittal of New Application (entered

April 16, 1999)), which is more than one year after the publication date of the Nolan reference.

The Specification states that "[t]his application is a continuation-in-part of U.S. Application Serial No. 09/062,330, filed on April 17, 1998 [now U.S. Patent No. 6,897,031 B1], and U.S. Application Serial No. 09/157,748, filed on September 21, 1998 (Specification 1 (as amended September 24, 2004)).

Thus, to remove the statutory bar set by 35 U.S.C. § 102(b) against patenting claims anticipated or obviated by printed publications available more than one year prior to an application's filing date, Appellants' claimed subject matter must find support in Application Serial No. 09/062,330(‘330 application), filed on April 17, 1998, which issued as U.S. Patent No. 6,897,031 B1. (See also the Board's decision at pages 12 -14).

The Examiner finds: The 09/062330 (now US Patent 6,897,031) ('031 Patent) does not provide support for now [newl]y presented claim 37 in its entirety (cf. with the ‘330 application) and each of the elements, as alleged, of the claims as given in the new matter rejection above.

For example, the new claim to a “library of at least 10^3 vectors encoding different candidate agents”; “subjecting” the

population of cells to a physiological signal that stimulates a phenotype in cells in the absence of the candidate bioactive agents”; "at least 3 optical properties" as applied to the different claim cellular phenotypes and “sequencing of the nucleic acid encoding said candidate agent”.

The '031 patent teaches:

> …[A] method for screening for alterations in **exocytosis of a population of cells** (**not the now presently broad claimed physiological signal**). The cells are sorted by a FACS machine by assaying for alterations in at least three of the properties(**not optical properties, as broadly claimed for the broad physiological signal**) selected from the group consisting of light scattering, fluorescent dye uptake, fluorescent dye release, annexin granule binding, surface granule enzyme activity, and the quantity of granule specific proteins. Methods for screening for bioactive agents capable of modulating **exocytosis** in a cell are also described…. (**not sequencing**)('031 patent, e.g., abstract). (Emphasis and parenthetical statements provided).

As stated above to avoid the statutory bar set by 35 U.S.C. § 102(b), Appellants must find descriptive support for the rejected claims in a priority application filed less than one year after publication of the Nolan reference. In the instant case, only the '330 application, which issued as the '031 patent, and which is asserted as a continuation-in-part parent to this application, has such a filing date (Board at FF 15).

Appellants are also directed to the further responses of February 24, 2006, as relied upon by appellants above.

Thus, the presently claimed method is not supported in the '031 patent, which is a CIP thereof.

As to the four specific elements provided by appellants above e.g., library of 10^3 vectors present in the parent

application, the responses above under the new matter rejection are incorporated herein in its entirety. The cited section as support, for example, for library of 10^3 vectors in the parent application is no different from the instant application.

Specific argument directed to claim 41

Appellants present the same arguments for claim 41 as above. Appellants submit that explicit support for claim 41, which requires a library "of at least 10^6 vectors" is found in the priority application on line 20 of page 24. This section states that, in the context of a library, "at least 10^6 ..... different sequences are simultaneously analyzed in the subject methods". Thus, if the Board believes that the rejection of claim 37 should be maintained because the specification does not describe 10^3 vectors, the Board is requested to withdraw the new matter rejection of claim 41.

"Subjecting the population of cells to a physiological signal"

That the method can be done by subjecting a population of cells to a physiological signal is implicitly supported in the priority application at page 24, lines 24-27:

> one another. For example, the cells may be evaluated in the presence or absence of physiological signals, such as exocytic inducers (i.e., Ca+, ionomycin, etc.), hormones, antibodies, peptides, antigens, cytokines, growth factors, action potentials, or other cells (i.e. cell-cell contacts). In another example, the measurements of exocytosis are

Evaluating cells in the presence or absence of a physiological signal implicitly requires that the cells are subjected to a physiological signal. As such, "subjecting" a population of cells to a physiological signal is implicitly supported in the specification.

In reply, the same responses above for the instant method is applied herein given that the corresponding support in the priority application are the same as in the instant application.

Nolan in view of Jia-pinq and Uhr in view of Hide.

Appellants submit that this rejection is also predicated on the claims not being supported by earlier filed application serial no. 09/062,330, now issued as U.S. patent 6,897,031. The claims are submitted to be fully supported in the instant application and in parent application serial no. 09/062,330, now issued as U.S. patent 6,897,031 (see table). As such, the Fisher declaration antedates Nolan's publication date, and Nolan cannot preclude the patentability of the rejected claims.

In reply, The Fisher declaration under 35 U.S.C. § 1.131 does not overcome the 35 USC 103 rejection as the declaration has no effect on a 35 USC 103 based on 35 USC 102(b) rejection.

(11) Related Proceeding(s) Appendix

Copies of the court or Board decision(s) identified in the Related Appeals and Interferences section of this examiner's answer are provided herein.

For the above reasons, it is believed that the rejections should be sustained.

Respectfully submitted,

/Teresa Wessendorf/

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Supervisory Patent Examiner, Art Unit 1636

/Ashwin Mehta/

Primary Examiner